

# Role of Pharmacy Professionals in Gene Therapy Based on Adeno-Associated Viruses: Treatment of Hemophilia as a Template of Care

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## ABSTRACT

**Background:** Gene therapy using adeno-associated viruses (AAVs) has emerged as a promising approach for the treatment of genetic disorders, including hemophilia, a rare bleeding disorder. Recently approved AAV-based treatments for hemophilia, such as etranacogene dezaparvovec and fidanacogene elaparvovec, could provide long-term benefits by targeting the genetic basis of the condition. Nonetheless, the application of gene therapies presents several challenges that necessitate a multidisciplinary approach.

**Objectives:** To explore the challenges associated with AAV-based gene therapy and the role of pharmacy professionals in ensuring its safe and effective application, using treatment of hemophilia as a care model.

**Data Sources:** Relevant literature was identified through searches in the PubMed, Embase, and Google Scholar databases, with a focus on publications related to AAV-based gene therapy, hemophilia, and the involvement of pharmacy professionals.

**Study Selection and Data Extraction:** Peer-reviewed articles, clinical guidelines, and regulatory documents were selected based on their relevance to the clinical, logistical, and ethical dimensions of AAV-based gene therapy.

**Data Synthesis:** Pharmacy professionals are integral to the continuum of care for AAV-based gene therapy. Their responsibilities include product handling and preparation, patient education, medication management, and long-term safety monitoring. Furthermore, pharmacy professionals can help address challenges such as financial obstacles, regulatory adherence, and ethical issues.

**Conclusions:** Using their expertise in medication management, patient education, and health system processes, pharmacy professionals can enhance the safety, effectiveness, and accessibility of AAV-based gene therapies for hemophilia, ultimately leading to better patient outcomes.

**Keywords:** adeno-associated virus, gene therapy, hemophilia, pharmacy professionals

## RÉSUMÉ

**Contexte :** La thérapie génique utilisant les virus adéno-associés (AAV) a émergé comme une approche prometteuse pour le traitement des maladies génétiques, notamment l'hémophilie, un trouble rare de la coagulation. Des traitements récents contre l'hémophilie, approuvés et reposant sur les AAV, tels que l'étranacogène dezaparvovec et le fidanacogène elaparvovec, pourraient offrir des bienfaits à long terme en ciblant la cause génétique de la maladie. Néanmoins, l'application de ces thérapies géniques s'accompagne de plusieurs défis nécessitant une approche multidisciplinaire.

**Objectif :** Étudier les défis associés à la thérapie génique basée sur les AAV, ainsi que le rôle des professionnels de la pharmacie pour s'assurer de son administration sécuritaire et efficace, en prenant le traitement contre l'hémophilie comme exemple de prise en charge.

**Sources des données :** La littérature pertinente a été identifiée à l'aide de recherches effectuées sur PubMed, Embase et Google Scholar, en se concentrant sur les publications portant sur la thérapie génique basée sur les AAV, l'hémophilie et l'implication des professionnels de la pharmacie.

**Sélection des études et extraction des données :** Des articles évalués par des pairs, des guides de pratique clinique et des documents réglementaires ont été sélectionnés selon leur pertinence par rapport aux dimensions cliniques, logistiques et éthiques de la thérapie génique basée sur les AAV.

**Synthèse des données :** Les professionnels de la pharmacie jouent un rôle essentiel dans le continuum des soins lié à la thérapie génique basée sur les AAV. Leurs responsabilités comprennent la manipulation et la préparation du produit, l'éducation des patients, la gestion des médicaments ainsi que le suivi de l'innocuité à long terme. De plus, ils peuvent contribuer à relever divers défis, tels que les obstacles financiers, le respect de la réglementation et les enjeux éthiques.

**Conclusions :** Grâce à leur expertise en gestion des médicaments, en éducation des patients et dans les processus des systèmes de santé, les professionnels de la pharmacie peuvent améliorer la sécurité, l'efficacité et l'accessibilité des thérapies géniques basées sur les AAV pour le traitement de l'hémophilie, contribuant ainsi à de meilleurs résultats pour la santé des patients.

**Mots-clés :** virus adéno-associé, AAV, thérapie génique, hémophilie, professionnels de la pharmacie

## INTRODUCTION

Gene therapy has emerged as a novel approach for the treatment of genetic disorders, offering the potential to address the root cause of inherited conditions.<sup>1</sup> The concept of using gene therapy to correct genetic abnormalities was introduced in 1972 in an article in the journal *Science*.<sup>2</sup> Since then, the field of gene therapy has evolved considerably, and various types of gene therapy have been explored.<sup>1</sup>

Gene therapy mediated through adeno-associated virus (AAV) has been studied for rare genetic disorders.<sup>3</sup> AAV vectors are engineered viral particles that deliver therapeutic segments of genes derived from human DNA sequences. These recombinant AAV vectors have been studied for gene therapy applications because of their favourable properties, including their ability to infect both dividing and nondividing cells, their low pathogenicity, and their long-term gene expression, in addition to being nonreplicating vectors.<sup>3,4</sup> As of June 2025, 4 AAV-based gene therapies had gained regulatory approval for use in Canada (Table 1): a pair of AAV-based therapies for hemophilia B (etranacogene dezaparvovec and fidanacogene elaparvovec), one therapy for retinal dystrophy (voretigene neparvovec), and one for spinal muscular atrophy (onasemnogene abeparvovec).<sup>5</sup> More than 200 investigational AAV-based gene therapies are in various stages of clinical trials.<sup>6</sup>

Although the approval of AAV-based gene therapies provides renewed hope for the treatment of hemophilia and other rare inherited diseases, it also creates regulatory and ethical challenges and safety concerns.<sup>7</sup> These challenges necessitate a new paradigm in health care delivery, one that emphasizes the importance of a multidisciplinary team approach. Practising at the intersection of medicine, science, and patient care, pharmacy professionals play an important role in ensuring the safe, effective, and efficient delivery of AAV-based gene therapy to patients with hemophilia.<sup>8,9</sup> Pharmacy professionals are well positioned to facilitate the successful implementation of gene therapy across the continuum, from pretreatment preparation through treatment administration to post-treatment monitoring.<sup>8,9</sup>

In this review article, we discuss the critical role of pharmacy professionals in the successful implementation of AAV-mediated gene therapy, using hemophilia as a

model. The article explores key considerations, challenges, and emerging trends, emphasizing the importance of pharmacy expertise across the continuum of care, including the implications of gene therapy approval for pharmacy professionals' scope of practice.

## METHODS

The topic for this article was determined through a needs assessment performed for a program accredited by the Canadian Council on Continuing Education in Pharmacy (CCCEP), entitled "DECODED: Unraveling the Applications of Gene Therapy for Pharmacy Professionals", which was developed for the Canadian Society of Hospital Pharmacists (now the Canadian Society of Healthcare-Systems Pharmacy) and sponsored by Pfizer Canada ULC.

A literature review was conducted to support the recommendations put forth through the educational program. Relevant literature was identified through searches in the PubMed, Embase, and Google Scholar databases, with a focus on publications related to AAV-based gene therapy, hemophilia, and the involvement of pharmacy professionals. Peer-reviewed articles, clinical guidelines, and regulatory documents were selected based on their relevance to the clinical, logistical, and ethical dimensions of AAV-based gene therapy.

This narrative review presents findings from the literature review and highlights some of the key recommendations from the educational program.

## TREATMENT OF HEMOPHILIA AS A BLUEPRINT FOR GENE THERAPY

### Current Hemophilia Landscape in Canada

Hemophilia is a rare inherited bleeding disorder caused by mutations in the genes encoding clotting factor VIII (the *F8* gene for hemophilia A) or IX (the *F9* gene for hemophilia B). Without sufficient concentrations of these blood-clotting proteins, individuals with hemophilia experience prolonged bleeding episodes that can lead to serious complications and reduced quality of life.<sup>10</sup> In Canada, hemophilia A affects approximately 1 in 5600 individuals, while hemophilia B affects approximately 1 in 25 600 individuals.<sup>11,12</sup>

**TABLE 1. Gene Therapies Based on Adeno-Associated Virus Approved by Health Canada<sup>a,b</sup>**

Product	Gene	Indication	Approval Date
Voretigene neparvovec	<i>RPE65</i>	Retinal dystrophy	October 13, 2020
Onasemnogene abeparvovec	<i>SMN1</i>	Spinal muscular atrophy	December 15, 2020
Etranacogene dezaparvovec	<i>FIX-R338L</i>	Hemophilia B	October 23, 2023
Fidanacogene elaparvovec	<i>FIX-R338L</i>	Hemophilia B	December 27, 2023

<sup>a</sup>Information is current as of June 2025.

<sup>b</sup>Retrieved from Health Canada's Notice of Compliance database.<sup>5</sup>

Both forms of the disorder show an X-linked recessive pattern of inheritance and are thus more common in males.<sup>10</sup>

The current standard of care for patients with hemophilia involves factor replacement therapy with regular infusions of clotting factor concentrates. Although factor replacement therapy can be used to prevent and manage bleeding episodes, it imposes a considerable burden on patients and health care systems and necessitates lifelong treatment, because it does not address the underlying genetic cause.<sup>13-16</sup> Additional limitations of factor replacement therapy include the need for frequent IV infusions, the risk of developing inhibitors against the infused factor, and the high cost.<sup>13-16</sup>

Bispecific antibodies, such as emicizumab and concizumab, are approved as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia. However, these agents do not eliminate breakthrough bleeding, and repeated treatments are required.<sup>17,18</sup> The frequency of administration of bispecific antibodies ranges from weekly to every 4 weeks, whereas prophylactic factor replacement therapy is typically administered 3 or 4 times per week for hemophilia A or 2 times per week for hemophilia B.

In addition, physical therapy, pain management, and joint treatments are used to prevent or manage complications associated with hemophilia; however, these represent only symptomatic management and further increase the treatment burden.<sup>13-15</sup>

### Approved AAV-Based Gene Therapies for Hemophilia

Gene therapy has emerged as a novel approach to address the root cause of hemophilia and other genetic disorders. This approach, called gene replacement therapy, involves IV infusion of genetically modified AAV vectors that carry functional copies of the defective gene (in this context, the *F8* gene for hemophilia A or the *F9* gene for hemophilia B).<sup>19</sup> Once in the body, the AAV vectors deliver the therapeutic gene into hepatocytes, which are responsible for the production of clotting factors. This process enables the patient's hepatocytes to produce and secrete the missing clotting factor into the circulation, restoring normal hemostasis and preventing or reducing bleeding episodes.<sup>19</sup> Currently, 2 AAV-based gene therapy products are approved by Health Canada for the treatment of hemophilia B: etranacogene dezaparvovec and fidanacogene elaparvovec (Table 1).

Etranacogene dezaparvovec is an AAV-based (serotype AAV5) gene therapy approved for the treatment of adults ( $\geq 18$  years) with hemophilia B who rely on routine prophylactic therapies to prevent or reduce bleeding episodes.<sup>20</sup> In the phase 3 HOPE-B trial (ClinicalTrials.gov identifier: NCT03569891), 54 adult males ( $\geq 18$  years) with severe or moderately severe hemophilia B received a single infusion of etranacogene dezaparvovec.<sup>21</sup> Compared with factor IX prophylaxis, infusion of etranacogene dezaparvovec

resulted in a reduced annualized bleeding rate (relative risk [RR] 0.36, 95% confidence interval [CI] 0.20 to 0.64,  $p < 0.001$ ), increased factor IX activity (by 34.3 [95% CI 29.5 to 39.1] percentage points,  $p < 0.001$ ), and reduced usage of factor IX concentrate (mean decrease of 248 825 IU per year per participant in the post-treatment period,  $p < 0.001$ ).<sup>21</sup> No serious treatment-related adverse events or deaths were observed during the study period. The most common adverse event, occurring in 16.7% of participants, was increased alanine transaminase (ALT) necessitating supportive care with corticosteroids.<sup>21</sup>

Fidanacogene elaparvovec is an AAV-based (serotype AAVRh74) gene therapy approved for the treatment of adults ( $\geq 18$  years) with moderately severe to severe hemophilia B who are negative for neutralizing antibodies to AAV serotype Rh74.<sup>22</sup> In the phase 3 BENEENE-2 trial (ClinicalTrials.gov identifier NCT03861273), 45 adult males ( $\geq 18$  years) with moderately severe to severe hemophilia were given a single infusion of fidanacogene elaparvovec.<sup>22</sup> Compared with factor IX prophylaxis, infusion of fidanacogene elaparvovec resulted in reduced annualized bleeding rate (treatment difference  $-2.34$ , 95% CI  $-4.97$  to  $0.29$ ), reduced need for factor replacement therapy (treatment difference  $-54.37$ , 95% CI  $-63.64$  to  $-45.10$ ), and sustained expression of factor IX.<sup>22</sup> The most common adverse events were increased serum transaminase concentration (in 46.6% of participants), nasopharyngitis (18.3%), and headache (16.6%).<sup>22</sup>

The therapeutic efficacy of AAV-based gene therapies for hemophilia depends not only on the vector delivery system but also on the regulatory elements that control transgene expression. Following IV administration, AAV vectors are distributed throughout the body and are taken up by multiple tissues, including the liver, skeletal muscle, and heart.<sup>23</sup> However, both etranacogene dezaparvovec and fidanacogene elaparvovec use liver-specific promoter elements to direct selective expression of the factor IX transgene in hepatocytes, which are responsible for the production of clotting factors. Etranacogene dezaparvovec employs a liver-specific LP1 promoter, which is derived from the hepatitis B virus and provides robust, hepatocyte-targeted expression.<sup>20</sup> Similarly, fidanacogene elaparvovec uses a liver-specific promoter, ApoE/hAAT, to ensure preferential transgene expression in hepatocytes, minimizing off-target expression in other tissues.<sup>22</sup> This hepatocyte-specific targeting is crucial for achieving therapeutic factor IX levels while reducing the risk of immune responses that might occur with broader tissue expression patterns.<sup>24</sup> Although AAV uptake occurs in multiple tissues, the off-target tissue distribution of these hemophilia B gene therapies has not been associated with significant clinical problems in clinical trials to date.<sup>20-22</sup> The inclusion of liver-specific promoters minimizes transgene expression in nonhepatic tissues, thereby reducing the potential for adverse effects related to ectopic factor IX production. However, the biodistribution to multiple organs

may contribute to immune responses against the AAV capsid, which can limit treatment efficacy and preclude repeat dosing with the same vector serotype.<sup>20-22</sup>

### Key Challenges with AAV-Based Gene Therapies for Hemophilia

Despite promising results from clinical trials of AAV-mediated gene therapies for hemophilia, several challenges remain. Although gene therapy aims to provide long-lasting benefits, long-term data on its durability and potential adverse effects are still needed. Factors such as vector instability, immune responses, and epigenetic silencing may limit the long-term expression of the transgene, potentially necessitating complementary treatments such as factor IX prophylaxis.<sup>25</sup>

Gene-related therapies have other key challenges. Notably, they are very expensive. Beyond the financial challenges for health care facilities, paying agencies, and, potentially, the patient and family,<sup>26,27</sup> in Canada, the lack of a well-defined regulatory framework for approval of these therapies, for post-marketing surveillance, and for cost-benefit monitoring is a consideration.<sup>26,28,29</sup> Furthermore, various ethical and equity concerns require consideration.<sup>26,30</sup> These challenges are discussed further in the section entitled “Need for a New Paradigm” (below).

Pre-existing immunity to AAV vectors or the transgene may render AAV-based gene therapy available to only a small portion of patients with hemophilia.<sup>31,32</sup> In clinical trials for fidanacogene elaparvec, trial eligibility criteria specified that all patients be screened for neutralizing antibodies to AAVrh74var using a cell-based antibody-mediated neutralization assay (transduction inhibition assay). In the global BeneGene-1 lead-in study, 61.1% of screened patients were positive for neutralizing antibodies (titer  $\geq$  1:1) and were therefore excluded.<sup>22</sup> Moreover, potential immune responses triggered by the vector or transgene can limit the durability of gene therapy and make redosing with the same AAV vector impossible.<sup>31,32</sup>

Although no cases of treatment-emergent hepatocellular carcinoma have been reported in clinical trials of AAV-based gene therapy for hemophilia, the theoretical risk of insertional mutagenesis and carcinogenicity remains a concern. Studies in animal models have identified common integration sites for AAVs near active transcription units and CpG islands and have shown that preferences for integration in specific sites vary across different species.<sup>33</sup> Despite evidence of near-random AAV integration in cell lines and animal models and evidence of AAV genotoxicity in neonatal mice studies, no confirmed genotoxic events have been reported in humans to date.<sup>33</sup> Longer follow-up studies are needed to understand AAV integration in humans and its implications for patient safety and treatment efficacy.

Variability in transgene expression is another challenge in AAV-mediated gene therapy for hemophilia. A clinical

trial of AAV5-based gene therapy for hemophilia A showed high variability in the therapeutic response and factor VIII activity. Median factor VIII activity at weeks 49 to 52 was 40 IU/dL or greater in 38% of patients, at least 5 IU/dL and less than 40 IU/dL in 50% of patients, less than 5 IU/dL in 12% of patients, and less than 3 IU/dL in 9% of patients.<sup>34</sup> Although the causes of this variability in endogenous expression and clinical outcomes are not fully understood, factors such as vector dose, route of administration, and individual patient characteristics may influence the level and duration of transgene expression.<sup>34</sup>

Hepatotoxicity is a common complication of AAV-mediated gene therapy and increases the treatment burden for patients with hemophilia.<sup>35</sup> Immune reactions after gene therapy could lead to hepatotoxicity and transaminitis and may influence the efficacy of gene therapy.<sup>36</sup> This raises the need for frequent monitoring of ALT and aspartate aminotransferase (AST) levels and factor IX activity for several years after AAV-based gene therapy for hemophilia.<sup>20,22</sup> Infusion-related effects are another common safety concern in patients with hemophilia who undergo AAV-based gene therapy.<sup>37</sup> In clinical trials of etranacogene dezaparvec infusion in patients with hemophilia B, 33.0% of patients experienced infusion-related reactions, which were the most common treatment-emergent adverse events.<sup>20</sup>

## INVOLVEMENT OF PHARMACY PROFESSIONALS IN DELIVERY OF AAV-MEDIATED GENE THERAPY FOR HEMOPHILIA

### Product Handling and Preparation

Pharmacy professionals lead the procurement, storage, quality control, preparation, and disposal of gene therapy products. Their responsibilities include coordinating with manufacturers, ensuring timely availability of the gene therapy product, and implementing measures to maintain vector integrity and stability before use.<sup>8,38,39</sup> AAV vectors have specific storage requirements, such as ultra-low temperatures, to maintain their integrity and potency.<sup>40,41</sup> Pharmacy professionals are responsible for ensuring that these storage requirements are met, as any deviations can reduce the integrity and efficacy of the gene therapy product.<sup>8,9</sup>

The preparation of AAV gene therapy products for administration involves aseptic preparation and reconstitution in a controlled, classified aseptic environment, to prevent contamination, with appropriate infrastructure to minimize staff members' exposure to gene therapy products.<sup>8</sup> Certified pharmacy professionals are trained in aseptic techniques, quality control processes, and proper handling of therapeutic or hazardous products. As such, they are well positioned to establish appropriate handling and preparation procedures, including the use of personal protective equipment (PPE), aseptic techniques, and

biosafety cabinets.<sup>8,38,42</sup> Pharmacy professionals are also key to establishing procedures for safe disposal of gene therapy-related materials to minimize exposure risks for pharmacy staff.<sup>8,42</sup> Protocols for handling and preparing gene therapy products are needed to minimize the risk of occupational exposure, errors, or contamination that could compromise patient safety, therapeutic outcomes, and the safety of health care professionals.

Practical considerations for pharmacy departments include ensuring availability of the following: appropriate refrigeration and freezer units with backup power sources for product storage and thawing; frameworks for product ordering, reception, and transport of gene therapy products from the pharmacy to the preparation area and the administration site; necessary certifications for handling viral vectors; PPE, including gowns, gloves, and respiratory and eye protection (e.g., mask, goggles, and face shields); and spill kits and appropriate disposal containers.<sup>8,43</sup> In terms of evaluating the site's infrastructure, it is crucial to assess the capacity of the facility to accommodate the necessary clean room requirements, equipment, and storage units, as well as the ability to maintain the required environmental conditions for product storage and safe handling. This includes evaluating the availability of backup power sources to ensure continuous operation of refrigeration and freezer units. Because national guidelines and frameworks for the implementation of gene therapies are lacking, pharmacy professionals may play a crucial role in developing institutional protocols, policies, and standard operating procedures, as well as in establishing the appropriate infrastructure for the proper and safe preparation, handling, and disposal of gene therapy products, as well as for spill management and decontamination processes.

### **Patient Selection and Preparation for AAV-Based Gene Therapy**

Pharmacy professionals contribute to patient selection and screening for AAV-based gene therapy through verification of key eligibility criteria, including patient age ( $\geq 18$  years for both approved therapies), hemophilia B diagnosis with documented factor IX deficiency, and severity criteria (moderately severe to severe hemophilia).<sup>20,22</sup> Pharmacy professionals can develop comprehensive screening checklists that include assessment for contraindications (such as active hepatitis B or C infection), significant liver disease (ALT and AST  $> 2$  times the upper limit of normal), history of hypersensitivity reactions, and current immunosuppressive therapy.<sup>20,22,44,45</sup> For neutralizing antibody screening, pharmacists coordinate with laboratories to ensure appropriate sample collection, storage, and transport for cell-based transduction inhibition assays, with specific protocols for AAV5 (etranacogene dezaparvovec) and AAVRh74 (fidanacogene elaparvovec) serotypes. Liver function assessment protocols should include baseline

measurements of ALT, AST, total and direct bilirubin, alkaline phosphatase, and albumin.<sup>20,22,44,45</sup>

Effective patient and family education and counseling are essential for successfully implementing gene therapy and setting realistic patient expectations. In a survey of Canadians with hemophilia conducted by the Canadian Hemophilia Society, 43% of respondents indicated that a minimum factor VIII or IX expression of 40% to 100% of normal levels would convince them to be treated with gene therapy.<sup>46</sup> Moreover, 40% of patients reported expecting that the desired factor concentration would last their entire lives.<sup>46</sup> These findings suggest that many Canadians with hemophilia have unrealistic expectations for gene therapy, which reinforces the importance of pre-infusion counseling and the setting of realistic expectations. As part of the multidisciplinary care team preparing patients for AAV-based gene therapy, pharmacy professionals, with their expertise in medication management and patient communication, are well positioned to provide clear, comprehensive, and evidence-based counselling and education to patients with hemophilia and their family members.<sup>44,47</sup>

Patient and family education topics should include the mechanism of action, expected outcomes, anticipated benefits, potential risks, common adverse effects, monitoring requirements, vector shedding precautions, long-term follow-up considerations, necessary lifestyle changes (e.g., reduction of alcohol consumption, use of barrier contraception), and gene therapy access and coverage considerations.<sup>44,47</sup> Pharmacy professionals can develop standardized patient education materials, including visual aids explaining the mechanism of AAV gene delivery, infographic comparisons of gene therapy and conventional treatment burdens, and realistic timeline expectations showing factor IX expression patterns over months to years. Effective counselling scripts should address common patient questions, such as "Will I ever need factor IX again?", "Is this a cure?", and "What are the chances it will work for me?" Informed consent enhancement strategies include using teach-back methods to confirm patient understanding, providing written summaries of key risks and benefits in plain language, offering family counselling sessions to address concerns about genetic implications, and implementing cooling-off periods between initial consultation and treatment decisions to allow adequate time for consideration.

In collaboration with other health care providers, pharmacy professionals can lead the development of patient support programs tailored to the needs and considerations of gene therapy recipients. Moreover, in preparing patients with hemophilia for gene therapy, pharmacy professionals collaborate with the team in the selection and correct dosing of prophylactic and supportive care medications associated with gene therapy, including immunosuppressants and adjunctive therapies.<sup>8,9,48</sup>

## Administration and Monitoring

Pharmacy professionals can take the lead in developing standardized protocols and guidelines for the safe and effective administration of gene therapy, based on their expertise in medication management, dosing, and administration protocols.<sup>8,9,44</sup> Pharmacy professionals can also provide guidance during the infusion of AAV gene therapy products, ensuring that therapy administration is carried out correctly and in accordance with established protocols.<sup>8,9,44</sup> This may include monitoring and managing infusion-related adverse events and complications.<sup>8,9,44,49</sup> They also play a key role in establishing and implementing protocols for post-infusion monitoring of concentrations of the clotting factor, liver enzymes, and total bilirubin, which are essential for assessing therapeutic response and risk of hepatotoxicity.<sup>8,9,44</sup>

## ROLE OF PHARMACY PROFESSIONALS IN PHARMACOVIGILANCE AND LONG-TERM MONITORING

The long-term safety of gene therapies and the durability of transgene expression are unknown, which emphasizes the importance of long-term monitoring of patients after AAV-based gene therapy.<sup>50</sup> Long-term follow-up considerations include monitoring for adverse events, educating patients and families on potential long-term adverse effects, and monitoring adherence to post-infusion medications and lifestyle adaptations (e.g., use of barrier contraception and reduction of alcohol consumption). As part of the treatment team, pharmacy professionals may be involved with registries (e.g., gene therapy module of the Canadian Bleeding Disorders Registry, Gene Therapy Registry of the World Bleeding Disorders Registry) to document outcomes and routinely export data to provincial and national databases.<sup>8,48,51</sup> Pharmacy professionals are well positioned to lead all these aspects of long-term follow-up of patients with hemophilia after AAV-based gene therapy.

In the immediate post-infusion period (first 12 weeks), patients require weekly monitoring of liver function tests (ALT, AST, total bilirubin) and factor IX activity levels to detect early hepatotoxicity and to assess initial therapeutic response.<sup>20,22</sup> During the intermediate phase (3 months to 2 years), monitoring frequency can be reduced to monthly for the first 6 months, then every 3 months, with a focus on sustained factor IX expression, liver enzyme stability, and clinical bleeding outcomes. Long-term monitoring (beyond 2 years) should occur every 6 to 12 months and should include comprehensive assessments of factor IX activity, complete blood count, comprehensive metabolic panel, and screening for potential late-onset adverse events, such as hepatocellular carcinoma, through imaging studies

and  $\alpha$ -fetoprotein levels. Additional biomarkers of interest include anti-AAV antibodies, which indicate immune responses; inflammatory markers (C-reactive protein, interleukin-6), which are present during acute phases; and coagulation parameters beyond factor IX levels (such as activated partial thromboplastin time and thrombin generation assays), which can be measured to evaluate overall hemostatic function. Vector shedding could be monitored through polymerase chain reaction-based detection in bodily fluids during the first months after infusion, with contraceptive counselling during this period.

The duration of patient follow-up after AAV-based gene therapy should be long enough to allow monitoring of patients for potential delayed adverse events according to the product type, the route of administration, the product's persistence and expression, the patient's expected survival, and the background rates of the events of interest.<sup>52</sup> Follow-up protocols should include a detailed plan for the schedule of patient visits, sampling methods, monitoring tests, clinical events of interest, detection and reporting of adverse events, causality analyses, and informed consent.<sup>52</sup>

Pharmacy professionals can also lead the establishment and implementation of institutional protocols, pharmacovigilance frameworks, and pharmacy checklists for patient-centric monitoring and for mitigating the long-term complications of AAV-mediated gene therapy. These frameworks should address the timing of monitoring and the parameters to be monitored, the management of potential immune responses and delayed adverse effects, monitoring of the impact of immune reactions on liver health and transgene expression, the use of immunosuppressive treatments (e.g., corticosteroids) when necessary, the patient's adherence to recommended lifestyle changes, and the adjustment of immunization schedules after gene therapy in patients who are also undergoing immunosuppressive treatments.<sup>52,53</sup>

Although there have been reports of serious adverse events following AAV-based gene therapy, reporting and monitoring of these adverse events have not been consistent among trials and clinics.<sup>54,55</sup> Pharmacy professionals are uniquely positioned to collaborate with regulatory agencies and manufacturers to report delayed therapy-related adverse events, to contribute to the evolving understanding of gene therapy safety profiles, to report any cases of hepatocellular carcinoma, to lead data collection and analysis efforts to assess real-world outcomes, and to inform future gene therapy development and utilization based on the collected data. Pharmacy professionals can also contribute to the long-term safety of gene therapy products by educating patients about the potential adverse events associated with gene therapy, the importance of prompt reporting of adverse events, and the need for ongoing monitoring and follow-up to assess the durability of gene therapy effects and potential late-onset adverse events.<sup>56,57</sup>

## NEED FOR A NEW PARADIGM: CHALLENGES AND OPPORTUNITIES FOR PHARMACY PROFESSIONALS

### Regulatory Challenges

Gene therapy products are subject to stringent regulations and oversight by various agencies, such as Health Canada, the US Food and Drug Administration, and the European Medicines Agency.<sup>26,58,59</sup> Integration of gene therapy into the Canadian health care system poses several regulatory challenges, including the lack of formal definition and classification of gene therapies, the limited capacity and expertise of regulatory bodies, the lack of pertinent legislation (or the presence of legislation that is not up to date with clinical practice), and insufficient post-market surveillance and data collection.<sup>26,28,29</sup>

Pharmacy professionals can ensure institutional preparedness and regulatory compliance by leading efforts to develop comprehensive guidelines and education programs for nursing, medical, and pharmacy staff and by collaborating with multidisciplinary teams to ensure a cohesive approach to gene therapy implementation.<sup>8,9</sup> By staying informed about the evolving regulatory framework relating to gene therapy, pharmacy professionals can also contribute to developing and updating institutional policies and procedures for the handling and administration of gene therapy, as well as liaising with regulatory bodies and professional organizations to stay current on guidelines and best practices.

### Ethical Challenges

Gene therapy raises unique ethical and social concerns that need to be addressed. Although current gene therapies for hemophilia target somatic cells and do not introduce heritable genetic modifications, the potential for germline editing raises ethical concerns about altering the human genetic makeup and implications for future generations.<sup>26,30</sup> There are also uncertainties regarding how to determine when there is sufficient preclinical evidence to initiate clinical trials and how to balance risks and benefits in dose selection, especially for irreversible and immunogenic gene therapies.<sup>26,30</sup>

Rigorous oversight and public discourse are needed to address concerns related to germline editing in patients undergoing gene therapy.<sup>60,61</sup> Pharmacy professionals can enhance informed consent-related processes by ensuring that patients and their families understand the risks, benefits, and long-term implications of AAV-mediated gene therapy and addressing concerns about germline modifications.<sup>62</sup> They must also collaborate with clinicians to develop fair and transparent patient selection criteria that consider both medical and ethical factors.<sup>63</sup> In collaboration with bioethicists and other stakeholders, pharmacy professionals can develop policies and guidelines that balance the potential benefits of gene therapy with ethical principles and societal values.<sup>64,65</sup>

### Financial Challenges and Equitable Access

Gene therapy raises concerns about equitable access and coverage of the associated high costs.<sup>26,27</sup> The high cost of gene therapies, particularly those targeting rare diseases, reflects the substantial investment required to develop and manufacture AAV-mediated gene therapy products.<sup>66,67</sup> In Canada, etranacogene dezaparvovec and fidanacogene elaparvovec each cost approximately \$4 million to \$5 million per treatment.<sup>68,69</sup> These one-time treatment costs must be considered in the context of the lifelong expenses associated with conventional factor IX prophylaxis, which can range from about \$322 000 to \$492 000 annually per patient, depending on disease severity and treatment regimen.<sup>68,69</sup> Financial challenges associated with the integration of gene therapy into the Canadian health care system include limited coverage, budget constraints, lack of gene therapy-specific guidelines and frameworks from health technology assessment bodies, and uncertainties about the efficacy, long-term safety, and cost-effectiveness of AAV-based gene therapies.<sup>26,27</sup>

Pharmacy professionals can reduce the health care costs of gene therapy by conducting pharmacoeconomic analyses and evaluating the cost-effectiveness of gene therapy compared to traditional treatments.<sup>70</sup> Factors to consider in pharmacoeconomic evaluations include the initial acquisition costs of gene therapy products, which can be substantial but may provide long-term benefits; the potential reductions in long-term health care costs associated with avoiding complications, hospitalizations, and ongoing traditional treatments; the value of improved quality of life and functional abilities for patients receiving gene therapy; and the broader economic implications of gene therapy, such as increased productivity and reduced caregiver burden.<sup>71-73</sup>

Pharmacy professionals can work with payers, health economists, health care administrators, patient advocacy groups, and other stakeholders to explore strategies for improving affordability and to develop reimbursement strategies to ensure that patients who could benefit from gene therapy have equitable opportunities to receive these treatments.<sup>74-76</sup> Pharmacy professionals can also be vital in navigating the complex landscape of coverage and reimbursement for AAV-mediated gene therapy. This work includes collaborating with payers to develop appropriate coverage policies, advocating for fair reimbursement rates, and assisting patients in accessing available financial assistance programs.<sup>77,78</sup> In addition, having trained pharmacists for on-site product preparation under aseptic conditions could enhance the ability of hospitals to deliver gene therapies and address some of the concerns about equitable access.<sup>79,80</sup>

### Collaborative Care Models

The successful implementation of gene therapy requires close collaboration among various health care professionals, each contributing their unique expertise and perspective

(Figure 1). Pharmacy professionals play a pivotal role in this multidisciplinary team, working closely with hematologists at infusion sites in patient selection, treatment planning, dose calculations, and monitoring of clinical outcomes, and with nurses and hematologists at referral or follow-up sites in coordination of care transitions, patient education (e.g., managing expectations of patients and caregivers), follow-up protocols (including adherence to lifestyle modifications), monitoring for complications of immunosuppression, assessment of eligibility and reimbursement requirements, and performance of post-infusion monitoring. In collaboration with hepatologists, pharmacy professionals can contribute to post-infusion monitoring and educating patients about long-term liver health. Pharmacy professionals can also liaise with regulatory and compliance experts to ensure adherence to relevant laws, regulations, and institutional policies governing gene therapy. Moreover, together with bioethicists and patient advocates, pharmacy professionals can help address ethical considerations, promote patient autonomy, and ensure equitable access to gene therapy.<sup>8,44,81</sup>

Patients require frequent and long-term follow-up after gene therapy for hemophilia, which can add to the burden of this disease for patients and their care partners.<sup>36,82</sup> The preparation of patients and their families for gene therapy and the post-administration monitoring phase could be enhanced through the use of telehealth and remote monitoring platforms.<sup>83</sup> Pharmacy professionals must be prepared to use these tools to facilitate patient follow-up, monitor adverse events, and optimize therapeutic outcomes.

## CONCLUSION

The recent approval of AAV-mediated gene therapy is a significant advancement in hemophilia treatment. The adoption of these new therapies requires a multidisciplinary effort, with pharmacy professionals playing a vital role at various stages of the process. From ensuring regulatory compliance and ethical oversight to managing the handling, preparation, and administration of gene therapy products, pharmacy professionals contribute their expertise to

optimize patient safety and therapeutic outcomes. Their involvement in patient education, counselling, and long-term monitoring is also important for managing expectations, promoting adherence, and evaluating the durability and potential adverse effects of gene therapy. Furthermore, pharmacy professionals' contributions to performing pharmacoeconomic analyses, developing reimbursement strategies, and addressing access challenges are essential for navigating the complex financial landscape of gene therapies and ensuring equitable access for eligible patients.

Emerging developments in gene therapy are expected to expand the role of pharmacy professionals in the management of hemophilia. Next-generation AAV vectors with improved tissue specificity and reduced immunogenicity, redosing strategies enabled by immunomodulatory approaches, and advances in manufacturing, including point-of-care preparation technologies,<sup>84-86</sup> will require pharmacy professionals to continuously adapt their protocols and infrastructure. The integration of digital health tools, artificial intelligence-assisted monitoring systems, and telemedicine platforms could enhance remote patient monitoring capabilities and predictive adverse event detection.<sup>87-89</sup> In addition, advancements in potential CRISPR-based gene therapies<sup>90</sup> necessitate that pharmacy professionals prepare for the increased complexity of the hemophilia treatment landscape through ongoing education, specialized training programs, and scalable operational frameworks.

The evolving regulatory landscape is likely to expand the responsibilities of pharmacy professionals, necessitating targeted education and training programs. Specialized training requirements could include certification programs covering AAV vector biology, aseptic handling of viral vectors, biosafety protocols (e.g., spill management), pharmacovigilance, and ethical aspects of gene therapy (e.g., equity considerations, germline modification concerns). Professional development opportunities such as workshops on gene therapy counselling techniques, webinars on emerging vector technologies, and hands-on training for specialized storage and preparation equipment would be essential for maintaining competency. To enhance their impact, pharmacy professionals should engage in continued



**FIGURE 1.** Multidisciplinary team approach in gene therapy for hemophilia. Diagram showcasing the close collaboration of pharmacy professionals with various health care professionals involved in gene therapy care.

collaboration with other health care professionals and stakeholders, pursue specialized education and training in gene therapy, and advocate for proactive guidance and leadership from pharmacy organizations.

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